

Liquid concentrate for the preservation of cosmetic and pharmaceutical products

The invention relates to a liquid concentrate based on
5 3-iodo-2-propynyl butylcarbamate (IPBC) and to its use
in the preparation and preservation of cosmetic and
pharmaceutical products.

Preservatives are used in many products or systems with
10 an aqueous phase in order to avoid harmful and spoiling
effects, in particular microbial effects, on the
product. Important fields of use of preservatives are
cosmetic products, such as shampoos, shower gels and
bath gels, but also high-value care cosmetics, such as
15 creams, emulsions, lotions and gels. Preservatives are
also used in cleaning, care and hygiene products for
the home (e.g. antimicrobial hand cleansers) and body
care (e.g. toothpaste).

20 IPBC has of late played an ever greater role in the
preservation of such products. It is available as a
white powder and has the disadvantage that it is only
very sparingly soluble in water (approximately 0.1 g/l
at 20°C). In the solid form, it has performance
25 disadvantages with regard to handling and metering. For
this reason, industry prefers to fall back on liquid
products and is interested in a liquid IPBC form.

In addition, the colour of the products is assuming an
30 ever greater role. Colourless or pastel-coloured
products, which furthermore should have a high colour
stability, are increasingly desired.

For example, EP 0 757 518 is known, in accordance with
35 which combinations of IPBC with formaldehyde-depositing
compounds are used. A further example of known IPBC
formulations is EP 0 484 172, in which combinations of
IPBC with 1,3,5-tris(hydroxyethyl)hexahydrotriazine are

described. DE 100 34 138, which describes combinations of IPBC with phenoxyethanol, is also known.

5 IPBC is actually sufficiently soluble in most organic solvents and compatible with many active agents, additives and auxiliaries used in cosmetics, yet the colour stability of liquid concentrates still causes great problems, which can be put down to their low solubility in water and their active groups in the IPBC
10 molecule. Sensitivity to light, heat and oxidation are to be added, resulting in the formation of coloured decomposition products. Odour development is also frequently inadequate.

15 It is therefore an object of the present invention to make available a liquid product in the form of a liquid concentrate for the preservation of cosmetic and pharmaceutical products based on IPBC which is colour-stable, which, in addition to the pronounced fungicidal
20 action, also shows a very good bactericidal action, which also is stable with reference to the active agent content and which has good organoleptic properties.

A liquid concentrate for the preservation of cosmetic
25 and pharmaceutical products based on 3-iodo-2-propynyl butylcarbamate (IPBC) is proposed to achieve this object, which liquid concentrate is characterized in that it, in addition to IPBC, comprises a liquid carrier chosen from polyvalent alcohols, glycol esters
30 and glycol ethers or any mixture thereof and a stabilizer chosen from formic acid, formate salts and formate esters or any mixture thereof, no additional carboxylic acid chosen from benzoic acid, propionic acid, salicylic acid, sorbic acid, 4-hydroxybenzoic
35 acid, dehydroacetic acid and 10-undecylenic acid or a salt thereof being present.

The proportions of the individual components in the liquid concentrate given below in weight% refer to the

weight of the combined concentrate, unless otherwise specified.

5 It has surprisingly been shown that, through the combination of IPBC with a liquid carrier and one of the formic acid derivatives mentioned as stabilizer, a product is obtained which has a stable colour, a stable active agent and an acceptable odour, without the microbiological activity being reduced.

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In this connection, "colour-stabilizing action" means that the concentrate, optionally diluted with solvent or in the product to be preserved, is subject to no obvious colour change (e.g. turning brown) under
15 conventional storage conditions. Such a colour change can, for example, be monitored with known test methods (e.g. determination of the Hazen colour number or Gardner colour number).

20 The term "active agent stability" means that, under conventional storage conditions over a period of at least 4 weeks, preferably 3 months, no precipitate perceptible by the senses or no cloudiness appears in the concentrate. "Conventional storage conditions" is
25 to be understood, for example, as storage at ambient temperatures from 15 to 25°C in dry, ventilated spaces. However, the liquid concentrate according to the invention also exhibits an improved storage stability over the period mentioned at temperatures which are
30 clearly higher than conventional storage temperatures, preferably higher than 40°C (e.g. 50°C), which is particularly advantageous for use thereof in tropical regions.

35 The invention also relates to a process for the preparation of such a liquid concentrate and to the use of the liquid concentrate according to the invention in the preparation and/or preservation of cosmetic and pharmaceutical products.

The liquid concentrate according to the invention comprises IPBC, with reference to the total weight, in an amount of 0.01 up to 20 weight% of IPBC, preferably 5 0.1 up to 5 weight% of IPBC, especially 0.1 up to 2 weight% of IPBC and particularly preferably up to 1 weight% of IPBC.

The liquid concentrate comprises, as liquid carrier, a 10 polyvalent alcohol, in particular a diol, preferably a glycol and more preferably ethylene glycol, 1,2-propylene glycol, 1,3-propylene glycol, 1,2-butylene glycol, 1,3-butylene glycol, 1,4-butylene glycol, 1,2-pentanediol, 1,3-pentanediol, 1,4-pentane- 15 diol or 1,5-pentanediol, or a glycol ester or glycol ether, in particular an ethylene glycol, propylene glycol or butylene glycol, preferably diethylene glycol, triethylene glycol or a polyethylene glycol, or any mixture thereof. Triethylene glycol or 20 1,2-propylene glycol are particularly preferred.

The amount of liquid carrier present in the liquid concentrate according to the invention ranges, with reference to the total weight, from 30 to 99.989 25 weight%; it preferably amounts to at least 50 weight% and especially at least 95 weight%.

The stabilizer component of the liquid concentrate is chosen from formic acid, sodium formate, potassium 30 formate, formic acid propylene glycol mono- or diester or formate esters formed in situ or any mixture thereof, in particular formic acid. 85% or 98-100% formic acid can, for example, be used.

35 The stabilizer component is present therein in an amount of 0.001 to 20 weight%, preferably 0.05 to 10 weight%, more preferably still 0.05 to 5 or to 2 weight% and for example less than 2 or less than 0.5 weight% or even less than 0.2 weight%.

The liquid concentrate can comprise additional active agents, functional additives and/or auxiliaries.

5 Polybiguanide (frequently also described as polyhexamethylenebiguanide hydrochloride) and/or a polybiguanide salt is possible as additional active agent, preferably in an amount, with reference to the total weight, of 0.1 up to 20 weight%, more preferably up to 5 weight%, particularly preferably up to 2
10 weight% and most preferably up to 1 weight%. For example, a 20% polyhexamethylenebiguanide hydrochloride in anhydrous or virtually anhydrous grade can be used.

15 The weight ratio of IPBC to polybiguanide or polybiguanide salt is in a preferred embodiment 100:1 to 1:100, preferably 10:1 to 1:10 and more preferably 1:2 to 2:1.

20 In an additionally preferred embodiment, the concentrate comprises ≤ 1 weight% of IPBC, in particular 1 weight%, and ≤ 1 weight% of polybiguanide/polybiguanide salt, in particular 0.95 weight%.

25 Depending on the field of application, it may be advantageous if the liquid concentrate is either anhydrous or comprises water as auxiliary, the content of water then preferably amounting to, based on the total weight, 0.01 up to 10 weight%, more preferably up
30 to 5 weight%, more preferably still up to 4.5 or up to 4 weight%, particularly preferably up to 0.2 weight% (virtually anhydrous). The liquid concentrates are preferably anhydrous or virtually anhydrous.

35 The liquid concentrate can comprise, as additional active agent, in addition to or in place of the polybiguanide compound, a paraben, in particular methyl-, ethyl-, propyl- or butylparaben, a quaternary ammonium compound, in particular polyhexamethylene-

- biguanide or a salt thereof, a benzalkonium salt, in particular benzalkonium chloride, formaldehyde or a formaldehyde-depositing compound or a salt thereof, in particular dimethyloldimethylhydantoin (DMDMH),
- 5 imidazolidinylurea, diazolidinylurea, hexetidine, 5-bromo-5-nitro-1,3-dioxane (bronidox), 2-bromo-2-nitro-1,3-propanediol (bronopol), 1,3,5,7-tetraazaadamantane (hexamethylenetetramine), 4,4-dimethyl-1,3-oxazolidine, benzyl alcohol hemiformal, 5-ethyl-1-aza-
- 10 3,7-dioxabicyclo[3.3.0]octane, 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride or mixtures thereof, phenoxyethanol, phenoxypropanol, benzyl alcohol, a halogen compound, in particular dibromodicyanobutane (DBDCB), an amidine compound, in
- 15 particular hexamidine or dibromohexamidine, or a salt thereof, or an isothiazolone, in particular N-methylisothiazolone or N-octylisothiazolone, or any mixture of the abovementioned compounds.
- 20 Preferred antimicrobial active agents which can be used to improve the effectiveness and/or to broaden the spectrum of activity are o-phenylphenol and its salts, zinc pyrithione, inorganic sulphites and bisulphites, sodium iodate, dibromohexamidine and its salts,
- 25 triclocarban, 4-chloro-m-cresol, triclosan, 4-chloro-3,5-dimethylphenol, 2-hydroxy-4,4'-dichlorophenyl ether (e.g. Tinosan HP 100), polyhexamethylenediguanide and its salts, 1-(4-chlorophenoxy)-1-(imidazol-1-yl)-3,3-dimethyl-2-butanone, 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone and its monoethanolamine
- 30 salt, 1,2-dibromo-2,4-dicyanobutane, bromochlorophen, 5-chloro-2-methyl-3(2H)-isothiazolone, 2-methyl-3(2H)-isothiazolone, 2-benzyl-4-chlorophenol, 2-chloroacetamide, chlorohexidine and its salts, N-[(C₁₂-C₂₂)alkyltrimethyl]ammonium salts, hexamidine and its
- 35 salts, glutaraldehyde, silver chloride, benzethonium chloride, benzalkonium salts (e.g. benzalkonium chloride), or mixtures of the abovementioned compounds.

In addition, a large number of substances or combinations of substances can be used as additional functional additives, auxiliaries or active agents (cosmetic additives) for the basic formulation (in place of the acids mentioned below, the corresponding salts are optionally used). The additives can be anion-active or cation-active. Examples of additives are skin care substances and moisture-retaining factors (e.g. urea or Sensiva SC 50), complexing agents (e.g. EDTA), essential oils and natural extracts, amphoteric surfactants, surfactants, cleaning additives and disinfection active agents (e.g. cocoamidopropyl betaine), fragrances, antiacne or antidandruff active agents (e.g. octopirox and Lipacid C8G), fungicides, dyes, corrosion inhibitors, disinfection active agents and antiseptics (e.g. octenidine dihydrochloride), bitter principals (e.g. denatonium salts), screening agents (e.g. 2-phenylbenzimidazolesulphonic acid), deodorant active agents (e.g. zinc phenolsulphonate or Sensiva SC 50), oral care active agents (e.g. potassium monofluorophosphate), isothiazolones, carbohydrate compounds (e.g. alkylpolyglycosides, starch or cellulose derivatives and cyclodextrins), alkali metal chlorides (e.g. NaCl or KCl), anionic surfactants (e.g. lauryl ether sulphates), plant extracts and oils. Quaternary ammonium salts (e.g. cetyltrimethylammonium chloride or bromide, cetylpyridinium chloride or didecyldimethylammonium chloride) can be used as possible cation-active active agents.

Many of these cosmetic additives also have a multifunctional action. In some cases, synergistic increases in activity of the liquid concentrates according to the invention with the additives may also arise.

Additional additives, auxiliaries and/or active agents are, for example, thickeners, buffers, antifoaming

agents, solubility promoters, antistatic agents, polymers and/or antioxidants.

5 In individual cases, the type and amount of additional active agents can be established by a person skilled in the art in a simple and rapid manner by a few experiments, it being possible for the active agent system obtained, which includes the liquid concentrate according to the invention, to have a broad or also
10 very specific application potential.

The preparation of the concentrates is carried out by simple mixing. For example, the solid components are dissolved with stirring in the liquid components and
15 the additional additives and auxiliaries are stirred in homogeneously. The mixture is optionally heated (e.g. up to 50°C).

With regard to the preparation process, in which the
20 constituents are mixed with one another in any sequence, it is optionally advantageous for the liquid concentrate to be stirred or allowed to stand at an increased temperature for a period of time. This temperature treatment results in a surprisingly
25 increased stability. In the course of this, the mixture is advantageously, subsequent to the mixing together, held for 0.5 to 48 hours at a temperature of 30 to 70°C, optionally with stirring, in particular 30 up to 60°C, more preferably at 30 up to 50°C. For example, a
30 temperature treatment over 6 h at 50°C, 24 h at 40°C or 48 h at 30°C is possible. The higher the temperature, the shorter the period of time of the temperature treatment can be.

35 It is advantageous that the liquid concentrates according to the invention can be incorporated in the cosmetic and pharmaceutical products by simple dilution. This offers handling and cost advantages compared with the use of individual substances, which

are often powders or granules and have to be dissolved or dispersed before incorporation in the product to be preserved. Storage and transportation costs can also be reduced by the concentrate form.

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A further advantage is that the liquid concentrates according to the invention are suitable as solubility promoters for cosmetic additives with little or limited solubility in water or as solvents or carriers for various cosmetic additives.

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The liquid concentrate according to the invention preferably exists as a clear homogeneous solution. However, should precipitates possibly arise at a low pH in the concentrate or in predilutions, these can be reversibly dissolved by simple dilution or by correcting the pH. However, it is also possible to prepare the liquid concentrate as a homogeneous-disperse preparation, it being preferable in such cases to avoid relatively large amounts of crystallized active agents in the preparation. In addition, the liquid concentrate can exist in the form of a paste.

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In a preferred embodiment, an "aged" mixture of glycols and/or glycol ethers and formic acid is used as carrier/stabilizer combination. The expression "aged" means in this connection that combinations of glycols and/or glycol ethers and formic acid are held at an increased temperature (up to boiling point of the mixture) for a sufficiently long period of time, optionally with stirring, until the smell of formic acid has largely or completely disappeared. Ester formation between the formic acid and the glycol and/or glycol ether possibly occurs during this ageing, the exact structure of the compounds formed being unknown. Alternatively, glycol (ether) formates can also be dissolved in glycol and/or glycol ether and the combination can be used together with the IPBC.

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Liquid concentrates which smell very little or not at all of formic acid are particularly preferred.

The pH of the liquid concentrate is 1 to 10, preferably 3 to 7 and preferably 5 to 7 (measured after preparation of a fresh solution or emulsion with water). For example, the pH of a 2 weight% solution/emulsion in water ranges from 2.5 to 5.5 or approximately 3.

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The liquid concentrates according to the invention therefore have, in particular, the following advantages:

- liquid;
- 15 - concentrate form;
- handling and cost advantages;
- homogeneous;
- limpid;
- low viscosity;
- 20 - colourless to faintly coloured;
- odourless or virtually odourless;
- very good thermal stability;
- very good colour stability;
- very good active agent stability;
- 25 - broad spectrum of activity with improved (synergistic) effectiveness compared with known IPBC products;
- can, during the production of cosmetics, serve as solvent, solubility promoter or carrier for other ingredients (e.g. fragrance, or the like);
- 30 - safe - no residue risk upon use;
- stable at low temperatures, liquid and pumpable at low temperatures (even after 12 months at, e.g., -5°C); and
- 35 - miscible, compatible with a wide range of ingredients.

The liquid concentrates according to the invention are suitable for the preparation of cosmetic products, in

particular for leave-on products, such as creams, lotions, gels or moist wipes, the pH values of which generally range from 5 to 8, or for rinse-off products, such as shampoos, the pH values of which are generally
5 less than 7, in particular less than 6.

Furthermore, the liquid concentrates according to the invention are suitable as additive for pharmaceutical products and for washing, cleaning, care, body care and
10 hygiene products. In addition to the preservation, the concentrates according to the invention contribute to the antimicrobial effectiveness.

The invention is illustrated below by means of
15 examples.

Examples

In the examples and comparative examples, polybiguanide
20 was used as a 20 weight% product in water; i.e. 4.75 weight% of 20% polybiguanide corresponds to 0.95 weight% of active agent.

The following formulations were prepared by introducing
25 the liquid carrier, adding the IPBC and the polybiguanide and then stirring until a clear solution was formed. The stabilizer was then added and homogeneously distributed with stirring. Clear solutions were obtained by doing this.

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Example 1:

1.00	weight%	IPBC
4.75	weight%	20% Polybiguanide
2.50	weight%	98-100% Formic acid
35 91.75	weight%	Triethylene glycol

Example 2:

1.00	weight%	IPBC
4.75	weight%	20% Polybiguanide

0.50 weight% 97% Sodium formate
93.75 weight% 1,3-Butanediol

Example 3:

5 1.00 weight% IPBC
4.75 weight% 20% Polybiguanide
2.90 weight% Formic acid (85% in water)
91.35 weight% 1,2-Propylene glycol

10 **Example 4:**

0.95 weight% IPBC
4.75 weight% 20% Polybiguanide
2.20 weight% Formic acid (85% in water)
92.10 weight% 1,2-Propylene glycol

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Comparative Examples

Comparative Example 1:

1.00 weight% IPBC
20 4.75 weight% 20% Polybiguanide
94.25 weight% 1,2-Propylene glycol

Comparative Example 2:

1.00 weight% IPBC
25 4.75 weight% 20% Polybiguanide
94.25 weight% Triethylene glycol

Comparative Example 3:

1.00 weight% IPBC
30 4.75 weight% 20% Polybiguanide
1.0 weight% Glycolic acid
93.25 weight% Triethylene glycol

Comparative Example 4:

35 1.00 weight% IPBC
4.75 weight% 20% Polybiguanide
1.0 weight% Lactic acid (80-90%)
93.25 weight% Triethylene glycol

Comparative Example 5:

	1.00	weight%	IPBC
	4.75	weight%	20% Polybiguanide
	1.0	weight%	Benzoic acid (>99.5%)
5	93.25	weight%	Triethylene glycol

Comparative Example 6:

	1.00	weight%	IPBC
	4.75	weight%	20% Polybiguanide
10	1.0	weight%	Formic acid (98-100%)
	93.25	weight%	Phenoxyethanol

The examples according to the invention all showed good stability with regard to odour, colour and active agent, while the products of the comparative examples did not display sufficient stability with regard to odour, colour and active agent.

The results of these investigations are collated in Tables 1 and 2.

Table 1: Storage stability, low-temperature stability and colour stability of the liquid concentrates

		Example 1	Example 3	Example 4	Comparative Example 1
Appearance immediately after preparation		clear liquid/colourless	clear liquid/colourless	clear liquid/colourless	clear liquid/almost colourless
Zero values	Odour	pungent	pungent	pungent	almost neutral
	Colour number/Hazen	14	6	6	27
	IPBC (%)	1.00	0.96	0.92	0.98
	Polybiguanide (%)	0.97	0.94	0.98	0.98
3 Months storage in blue polyethylene bottles					
Appearance	All samples through all following storage conditions o.V. (clear liquids)				
-5°C	Odour	not pungent	not pungent	not pungent	almost neutral
	Colour number/Hazen	99	6	7	74
	IPBC (%)	0.98	1.00	0.94	0.98
	Polybiguanide	1.00	0.94	0.93	1.01
4°C	Odour	not pungent	not pungent	not pungent	almost neutral
	Colour number/Hazen	64	97	8	553
	IPBC (%)	0.98	0.99	0.93	0.98
	Polybiguanide	1.01	0.95	0.94	1.01
25°C	Odour	not pungent	not pungent	not pungent	almost neutral
	Colour number/Hazen	33	16	16	346
	IPBC (%)	0.97	0.97	0.89	0.88
	Polybiguanide	1.02	0.96	0.96	1.02
ATL (ambient temperature/light)	Odour	not pungent	not pungent	not pungent	almost neutral
	Colour number/Hazen	30	9	10	422
	IPBC (%)	0.97	0.97	0.95	0.87
	Polybiguanide	1.01	0.96	0.95	1.01
Window/South	Odour	not pungent	not pungent	not pungent	almost neutral
	Colour number/Hazen	78	22	21	773
	IPBC (%)	0.94	0.96	0.95	0.77
	Polybiguanide	1.02	0.97	0.97	1.02
40°C	Odour	not pungent	not pungent	not pungent	almost neutral
	Colour number/Hazen	189	568	495	560
	IPBC (%)	0.88	0.65	0.66	0.58
	Polybiguanide	1.04	1.01	1.00	1.03

Table 2: Storage stability, low-temperature stability and colour stability of liquid concentrates according to the invention

	Comparative Example 3	Comparative Example 4	Comparative Example 5	Comparative Example 6	Example 2
Appearance immediately after preparation	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless
Hazen colour number	7	9	9	5	5
Odour	characteristic	characteristic	characteristic	pungent	not pungent
IPBC content	0.98	1.01	1.03	1.01	1.00
After storage for 4 weeks at ambient temperature/light in a glass jar:					
Appearance	clear	clear	clear	clear	clear
Hazen colour number	> 1 000	> 1 000	> 1 000	> 1 000	5
Gardner colour number	6.4	6.4	5.8	0	0
Odour	o.V.	o.V.	o.V.	not pungent	o.V.
After storage for 4 weeks at +50°C in a glass jar:					
Appearance	clear	clear	clear	clear	clear
Hazen colour number	> 1 000	> 1 000	> 1 000	> 1 000	122
Gardner colour number	5.4	5.4	5.5	6.6	0.4
Odour	o.V.	o.V.	o.V.	not pungent	o.V.
IPBC content	0.76%	0.74%	0.72%	0.45%	0.96%
IPBC loss in %	22%	27%	30%	55%	4%

It follows from Tables 1 and 2 that the liquid concentrate according to the invention show a clearly improved stability.

5 For the colour stability investigations, the liquid concentrates were stored in clear glass and the Hazen or Gardner colour number (see test methods) was determined immediately after preparation on a freshly produced preparation, and also after the period of time
10 given and storage at the temperatures given.

Test methods:

The Hazen colour number (DIN-ISO 6271, also known as
15 "APHA method" or "platinum/cobalt scale") is defined as mg of platinum per 1 litre of solution. For the Hazen stock solution, 1.246 g of potassium hexachloro-platinate(IV) and 1.00 g of cobalt(II) chloride are dissolved in 100 ml of hydrochloric acid and made up to
20 1 000 ml with distilled water. The Hazen colour scale is used for assessing the colour of products which are almost limpid. It is graduated more closely in the light-yellowish region than the iodine colour scale and extends as far as limpid shades of colour.

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The Gardner colour number is defined in DIN-ISO 4630. The light-yellow Gardner colour numbers (1 to 8) are based on potassium chloroplatinate solutions and the colour numbers 9 to 18 on iron(III) chloride,
30 cobalt(II) chloride and hydrochloric acid solutions.

The respective concentrate was introduced into a cell and then the colour number was measured using a colorimeter of Lico® 200 type (Dr Lange GmbH, Berlin).

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The odour development was examined organoleptically. The odours were in each case assessed by 3 people.